# A Synthesis of Benzothiazoles and Indoles by Direct C(sp$^2$)–I Activation Catalyzed by Copper(II) on Silica-Coated Magnetite Nanoparticles

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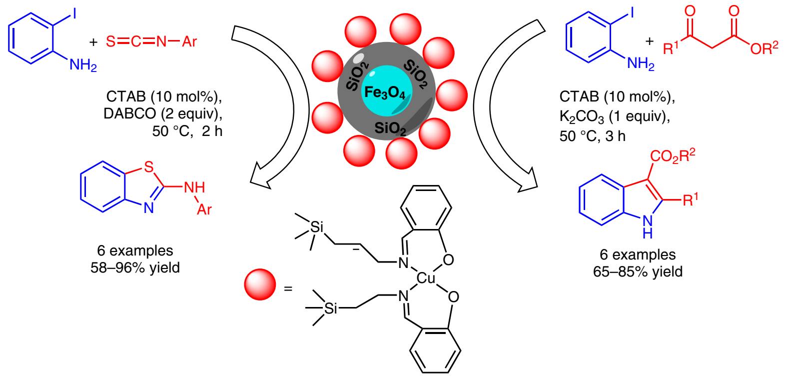

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**Abstract** *N*-Substituted 2-amino-1,3-benzothiazoles and 2,3-disubstituted indoles were prepared by C–S and C–C cross-coupling reactions of 2-iodoanilines with isothiocyanates or 1,3-dicarbonyl compounds, respectively, in the presence of magnetic nanoparticles functionalized with a copper(II)–Schiff base complex as an efficient and reusable catalyst.

**Key words** cross-coupling, benzothiazoles, indoles, copper, catalysis, Schiff bases

In recent years, several syntheses of various heterocyclic compounds such as pyrrole, indole, furan, or benzothiophene derivatives through cross-coupling reactions catalyzed by copper derivatives have been reported in the literature.[1] In a continuation of our work on heterogeneous catalysts and cross-coupling reactions,[2] we recently reported the synthesis of benzoate and carbamate derivatives through oxidative C–O coupling reactions in the presence of new magnetic nanoparticles functionalized with a copper–Schiff base complex.[2d] We therefore decided to examine this catalyst in carbon–halogen bond-activation reactions for the synthesis of 2,3-disubstituted indoles and *N*-substituted 2-amino-1,3-benzothiazole derivatives.

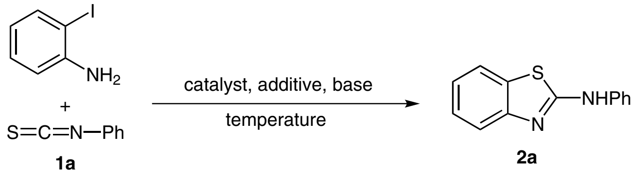
In an initial attempt, the cross-coupling reaction of 2-iodoaniline with phenyl isothiocyanate was probed in the presence of subequivalent amounts of the catalyst in water as a green solvent. To optimize the reaction conditions, various bases, additives, and amounts of catalyst were investigated. The best results were obtained by performing the reaction in the presence of 15 mg of the magnetic catalyst (containing 0.016 mmol copper), DABCO (2 equiv), and cetyltrimethylammonium bromide (CTAB, 10 mol%) at 50 °C for two hours (Table 1, entry 1).[3] Performing the reaction in the presence of various other additives (entries 8–10) and bases (entries 11–15) failed to improve the yield. Increasing the amount of catalyst (entry 5), CTAB (entry 6), or DABCO (entry 3), or raising the temperature (entry 16) similarly failed to improve the yield, as did decreasing the amount of DABCO or CTAB or lowering the temperature (entries 2, 17, and 4, respectively). None of the desired product was obtained in the absence of the magnetic catalyst, DABCO, or CTAB (entries 18–20).

With the optimized reaction conditions in hand, we extended our study to various other isothiocyanate derivatives **1**. We found that the reaction tolerates a variety of isothiocyanates containing either electron-withdrawing or electron-donating substituents. The reactions were generally clean and gave the desired products **3a**–**f** in moderate to excellent yields (Table 2).

A plausible mechanism for the reaction of 2-iodoaniline with isothiocyanate compounds has been proposed in the literature.[1j]

Following our successful synthesis of *N*-substituted 2-amino-1,3-benzothiazoles derivatives, we decided to evaluate the effect of this catalyst system in the cross-coupling reaction of 2-iodoaniline with 1,3-dicarbonyl compounds. For this purpose, we chose the reaction of 2-iodoaniline with methyl acetoacetate as a model reaction to determine the optimal conditions. Various additives, bases, and amounts of catalyst were studied, and the best results were obtained by performing the reaction in the presence of 20 mg of magnetic catalyst (containing 0.021 mmol copper), K$_2$CO$_3$ (1 equiv), and CTAB (10 mol%) at 50 °C for three hours to give an 85% yield of product **4a** (Table 3, entry 1).[4]

**Table 1** Optimization of Reaction Conditions for the Synthesis of Benzothiazole **2a**



| Entry | Catalyst (mg) | Additive (mol%) | Base (equiv) | Temp (°C) | Yield[a] (%) |
|---|---|---|---|---|---|
| **1** | **15** | **CTAB (10)** | **DABCO (2 equiv)** | **50** | **93** |
| 2 | 15 | CTAB (10) | DABCO (1.5 equiv) | 50 | 70 |
| 3 | 15 | CTAB (10) | DABCO (2.5 equiv) | 50 | 90 |
| 4 | 10 | CTAB (10) | DABCO (2 equiv) | 50 | 68 |
| 5 | 20 | CTAB (10) | DABCO (2 equiv) | 50 | 85 |
| 6 | 15 | CTAB (15) | DABCO (2 equiv) | 50 | 95 |
| 7 | 15 | CTAB (5) | DABCO (2 equiv) | 50 | 80 |
| 8 | 15 | TBAF (10) | DABCO (2 equiv) | 50 | 60 |
| 9 | 15 | TBAB (10) | DABCO (2 equiv) | 50 | 87 |
| 10 | 15 | SDS[b] (10) | DABCO (2 equiv) | 50 | 83 |
| 11 | 15 | CTAB (10) | $K_2CO_3$ (2 equiv) | 50 | 40 |
| 12 | 15 | CTAB (10) | $K_3PO_4$ (2 equiv) | 50 | trace |
| 13 | 15 | CTAB (10) | $Na_2CO_3$ (2 equiv) | 50 | 30 |
| 14 | 15 | CTAB (10) | py (2 equiv) | 50 | 45 |
| 15 | 15 | CTAB (10) | NaOH (2 equiv) | 50 | trace |
| 16 | 15 | CTAB (10) | DABCO (2 equiv) | 60 | 90 |
| 17 | 15 | CTAB (10) | DABCO (2 equiv) | 40 | 69 |
| 18 | – | CTAB (10) | DABCO (2 equiv) | 50 | – |
| 19 | 15 | CTAB (10) | – | 50 | – |
| 20 | 15 | – | DABCO (2 equiv) | 50 | trace |

[a] Isolated yield,
[b] SDS = sodium dodecyl sulfate

Increasing the amount of CTAB (Table 3, entry 6) and/or using another additive (entries 8–10) failed to improve the yield. Increasing the amount of $K_2CO_3$ (entry 3) or the catalyst (entry 5), or changing the base (entries 11–15) also failed to improve the yield, whereas decreasing the amount of base or catalyst (entries 2 and 4) led to reduced yields. In the absence of the catalyst, base, or additive, the model reaction failed to give the desired product (entries 18–20).

With the optimized reaction conditions in hand, we extended our study to a range of 1,3-dicarbonyl compounds **3b**–**f** (Table 4).

Catalyst recovery and reuse was evaluated for both reactions. After completion of the first reaction in both protocols, the catalyst was recovered by using an external magnet, washed with methanol, and oven dried at 100 °C overnight. The recovered catalyst could be used at least five consecutive times without significant loss in product yield (Figure 1).

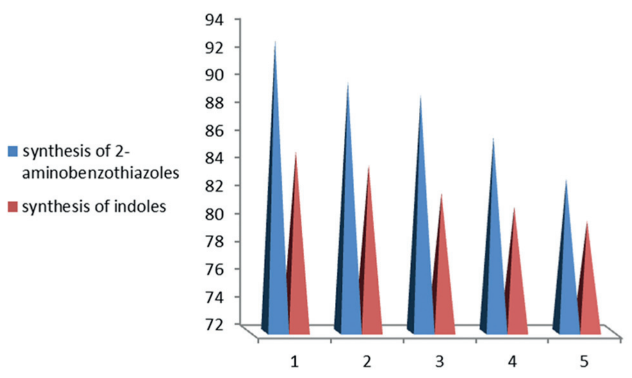
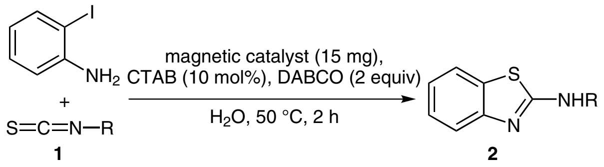


**Figure 1** Reusability of the catalyst

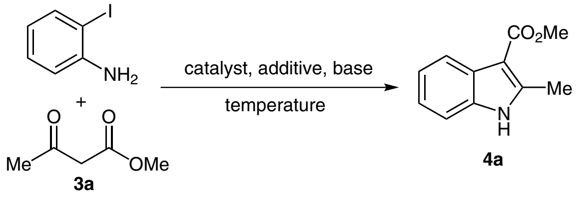
**Table 2** Synthesis of 2-Amino-1,3-benzothiazole Derivatives



| Entry | R | Products **2** | Yield[a] (%) | Ref. |
|---|---|---|---|---|
| 1 | Ph | **2a** | 93 | 1b,k |
| 2 | 4-$ClC_6H_4$ | **2b** | 71 | 1k |
| 3 | 4-Tol | **2c** | 89 | 1b,k |
| 4 | 4-$O_2NC_6H_4$ | **2d** | 96 | 1k |
| 5 | 4-$FC_6H_4$ | **2e** | 85 | 1k |
| 6 | Cy | **2f** | 58 | 1b |

[a] Isolated yield.

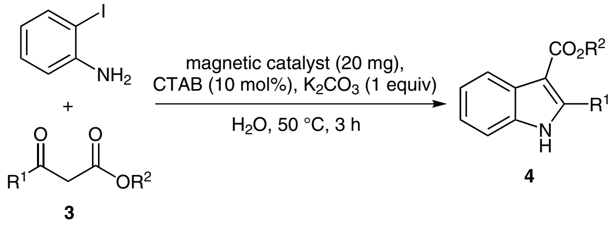
**Table 3** Optimization of the Reaction Conditions for the Synthesis of Indole **4a**



| Entry | Catalyst (mg) | Additive (mol%) | Base (equiv) | Temp (°C) | Yield[a] (%) |
|---|---|---|---|---|---|
| **1** | **20** | **CTAB (10)** | **$K_2CO_3$ (1 equiv)** | **50** | **85** |
| 2 | 20 | CTAB (10) | $K_2CO_3$ (0.5 equiv) | 50 | 56 |
| 3 | 20 | CTAB (10) | $K_2CO_3$ (1.5 equiv) | 50 | 81 |
| 4 | 15 | CTAB (10) | $K_2CO_3$ (1 equiv) | 50 | 69 |
| 5 | 25 | CTAB (10) | $K_2CO_3$ (1 equiv) | 50 | 85 |
| 6 | 20 | CTAB (15) | $K_2CO_3$ (1 equiv) | 50 | 85 |
| 7 | 20 | CTAB (5) | $K_2CO_3$ (1 equiv) | 50 | 73 |
| 8 | 20 | TBAF (10) | $K_2CO_3$ (1 equiv) | 50 | 55 |
| 9 | 20 | TBAB (10) | $K_2CO_3$ (1 equiv) | 50 | 68 |
| 10 | 20 | SDS (10) | $K_2CO_3$ (1 equiv) | 50 | 72 |
| 11 | 20 | CTAB (10) | DABCO (1 equiv) | 50 | 80 |
| 12 | 20 | CTAB (10) | $K_3PO_4$ (1 equiv) | 50 | 20 |
| 13 | 20 | CTAB (10) | $Na_2CO_3$ (1 equiv) | 50 | 35 |
| 14 | 20 | CTAB (10) | py (1 equiv) | 50 | 50 |
| 15 | 20 | CTAB (10) | NaOH (1 equiv) | 50 | trace |
| 16 | 20 | CTAB (10) | $K_2CO_3$ (1 equiv) | 60 | 85 |
| 17 | 20 | CTAB (10) | $K_2CO_3$ (1 equiv) | 40 | 70 |
| 18 | – | CTAB (10) | $K_2CO_3$ (1 equiv) | 50 | – |
| 19 | 20 | CTAB (10) | – | 50 | – |
| 20 | 20 | – | $K_2CO_3$ (1 equiv) | 50 | – |

[a] Isolated yield.

**Table 4** Synthesis of Indole Derivatives **4a–f**



| Entry | $R^1$ | $R^2$ | Products **4** | Yield[a] (%) | Ref. |
|---|---|---|---|---|---|
| 1 | Me | Me | **4a** | 85 | 1a |
| 2 | Et | Me | **4b** | 80 | 1a |
| 3 | *i*-Pr | Me | **4c** | 75 | 1a |
| 4 | *t*-Bu | Me | **4d** | 69 | 1a |
| 5 | Ph | Et | **4e** | 70 | 1a |
| 6 | Naphth | Et | **4f** | 65 | 1a |

[a] Isolated yield

After investigating the catalyst recovery, we examined the leaching of copper. For this purpose, we removed the catalyst with an external magnet ten minutes after the beginning of the reaction. We observed that the reaction did not subsequently reach completion, even after 24 hours. This clearly confirmed that no significant leaching of copper into the solvent had occurred after ten minutes. An additional study by inductively coupled plasma analysis confirmed that no leaching of the copper complex had occurred.

In summary, we have described a green and ecofriendly method for the synthesis of 2,3-disubstituted indoles or *N*-substituted-2-amino-1,3-benzothiazoles by cross-coupling reactions in the presence of magnetic nanoparticles functionalized with a Schiff base–copper complex as a catalyst. Ease of workup, the use of water as solvent, good yields, and short reaction times in comparison with other methods are the main advantages of these protocols.

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## Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561405.

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(3) ***N*-Substituted 1,3-Benzothiazol-2-amines 2a–f; General Procedure**
A mixture of the appropriate isothiocyanate **1** (1.1 equiv), 2-iodoaniline (1 equiv), CTAB (10 mol%), DABCO (2 equiv), and magnetic catalyst (15 mg) in $H_2O$ (4 mL) was stirred at 50 °C for 2 h then cooled to r.t. The catalyst was removed by using an external magnet, and the solution was extracted with EtOAc (3 × 10 mL). The extracts were dried ($MgSO_4$), filtered, and concentrated under vacuum to give a crude product that was purified by column chromatography.
***N*-Phenyl-1,3-benzothiazol-2-amine** (**2a**)
White solid; yield: 210 mg (93%); mp 157–160 °C. IR (KBr): 3459, 1635 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.02 (t, $^3J_{HH}$ = 7.2 Hz, 1 H), 7.61 (t, $^3J_{HH}$ = 7.2 Hz, 1 H), 7.30–7.41 (m, 3 H), 7.15 (d, $^3J_{HH}$ = 7.7 Hz, 1 H), 7.76–7.84 (m, 3 H), 10.48 (s, 1 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 118.2, 119.7, 121.5, 122.5, 122.8, 126.4, 129.5, 130.5, 141.2, 152.6, 162.1.

(4) **2,3-Disubstituted Indoles 4a–f; General Procedure**
A mixture of the appropriate 1,3-dicarbonyl compound **3** (1.1 equiv), 2-iodoaniline (1 equiv), CTAB (10 mol%), $K_2CO_3$ (1 equiv), and magnetic catalyst (20 mg) in $H_2O$ (4 mL) was stirred at 50 °C for 3 h then cooled to r.t. The catalyst was removed by using an external magnet, and the solution was extracted with EtOAc (3 × 10 mL). The extracts were dried ($MgSO_4$), filtered, and concentrated under vacuum to give a crude product that was purified by column chromatography.
**Methyl 2-Methyl-1*H*-indole-3-carboxylate** (**4a**)
Beige solid; yield: 160 mg (85%); mp 164–166 °C. IR (KBr): 3016, 1690, 1449, 1209, 10905 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 2.72 (s, 3 H), 3.93 (s, 3 H), 7.16–7.30 (m, 3 H), 8.08 (d, *J*= 7.7 Hz, 1 H), 8.67 (br s, 1 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 14.2, 50.8, 104.3, 110.4, 121.2, 121.7, 122.3, 127.2, 134.5, 144.2, 166.7.